

**REMARKS**

**I. Amendments to the Specification:**

The specification submitted with the Preliminary Amendment on March 21, 2002 has been amended to correct numerous clerical errors. A substitute specification conforming to the requirements set forth in 37 C.F.R. § 1.121(b)(3) and 37 C.F.R. § 1.125(b) is submitted herewith (*see, Appendix A*). Support for the amendments to the specification can be found in the application as originally filed. It is submitted that no new matter has been added by way of the instant amendments to the specification.

**II. Amendments to the Claims:**

Claims 22-34 were pending in the instant application.

Claims 23 and 24 have been canceled without prejudice or disclaimer of the subject matter claimed therein solely with the intent of expediting prosecution of the instant application. Applicants reserve the right to pursue the subject matter of claims 23 and 24 in this or future related applications.

Claims 22, 27-29 and 34 have been amended. Support for the amendments to claims 22 and 34 can be found throughout the specification as filed (*see, for example, page 22, paragraph [0067]; and page 43, paragraph [0134]*). Claims 27-29 have been amended to correct clerical errors.

Claim 35 has been newly added. Support for this new claim can be found for example, at page 15, paragraph [0042].

Upon entry of the instant amendment to the claims, claims 22 and 25-35 will be pending in the instant application.

**III. Objection:**

The Office Action objected to claims 22-34 as being drawn in part to a non-elected invention (*see, Office Action, page 3*).

In view of the finality of the Restriction Requirement, Applicants have amended claims 22 and 34 to delete reference to  $\gamma\delta$  T cell receptors. Accordingly, this objection has been rendered moot.

**IV. Rejection Under 35 U.S.C. § 112, Second Paragraph:**

The Office Action rejected claim 23 as being allegedly indefinite for reciting the phrase "low concentration" (*see, Office Action, page 3*).

Claim 23 has been canceled without prejudice or disclaimer of the subject matter recited therein. Accordingly, this rejection under 35 U.S.C. § 112, second paragraph, has been rendered moot.

**V. Rejection Under 35 U.S.C. § 112, First Paragraph, New Matter:**

The Office Action rejected claim 24 under 35 U.S.C. § 112, first paragraph, for purportedly lacking clear support in the specification for the limitation "wherein said TCR is stable at a concentration of about 20 mg/ml" (*see, Office Action, page 3*).

Claim 24 has been canceled without prejudice or disclaimer of the subject matter recited therein. Accordingly, this rejection under 35 U.S.C. § 112, first paragraph, has been rendered moot.

**VI. Rejection Under 35 U.S.C. § 112, First Paragraph, Scope:**

The Office Action rejected claim 33 under 35 U.S.C. § 112, first paragraph, for purportedly not being enabling for a soluble TCR linked to a therapeutic agent (*see, Office Actions, pages 4-8*). As part of this rejection, the examiner has stated that "*many thousand of drugs have shown activity in either cell and animal models but that only 39 have actually been shown to be useful for chemotherapy*" and that "*the refractory nature of cancer to drugs is well-known.*"

Applicants respectfully traverse this rejection. Applicants' claim 33 refers to a "therapeutic agent," and therefore does not encompass TCRs linked to agents that have previously been shown to be ineffective. Thus, the claim is intended to cover TCRs linked to effective therapeutic agents, the purpose of the TCR being to target the therapeutic agent to the site to be treated. Furthermore, Applicants respectfully assert that there is no basis for

the Office Action to contend that a therapeutic agent that has been shown to be effective in untargeted form will not be effective when targeted by virtue of being attached to a soluble TCR of the invention.

In light of the foregoing remarks, Applicants respectfully request that this rejection be reconsidered and withdrawn.

**VII. Rejections Under 35 U.S.C. § 102(b):**

The Office Action rejected claims 22-26 and 34 under 35 U.S.C. § 102(b), as allegedly being anticipated by Gregoire *et al.* (*see*, Office Action, pages 8-10) and Weber *et al.* (*see*, Office Action, pages 10-13).

Both Gregoire *et al.* and Weber *et al.* disclose chimeric soluble TCRs in which the respective TCR chains are linked to antibody κ chains. Specifically, Gregoire *et al.* and Weber *et al.* disclose TCRs of the following construction:

TCRV $\alpha$ -TCRC $\alpha$ -antibody κ chain

TCRV $\beta$ -TCRC $\beta$ -antibody κ chain

Applicants' claims 22 and 34 recite, in relevant part, that "the first dimerization peptide and the second dimerization peptide are specifically *heterodimerized* to form a *heterodimerization domain*" (emphasis added).

In contrast, the antibody κ chains of Gregoire *et al.* and Weber *et al.* are identical and therefore form *homodimers*.

The Federal Circuit has made clear that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference" *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2USPQ2d 1051, 1053 (Fed. Cir. 1987). Because, Gregoire *et al.* and Weber *et al.* do not teach each and every element of Applicants' claimed invention, neither of these references anticipates Applicants' claimed invention.

Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

### VIII. Rejections Under 35 U.S.C. § 103

(a) The Office Action rejected claims 22-27, 29 and 34 as purportedly being obvious under 35 U.S.C. § 103(a) over Chang *et al.*, in view of Gregoire *et al.*, Garboczi *et al.*, and Wulffing *et al.* (Office Action, pages 14-20).

Briefly, the Office Action alleges that Chang *et al.* disclose all the features of claims 22 and 34, except the absence of the interchain disulfide bond, and that Gregoire *et al.*, Garboczi *et al.*, and Wulffing *et al.* teach or suggest modifying Chang to omit the disulfide bond.

Applicants respectfully traverse this rejection for the reasons outlined in detail below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Applicants respectfully assert that the Office Action has not established a *prima facie* case of obviousness.

Applicants' claim 22 is directed to a recombinant soluble T cell receptor (TCR) which comprises a TCR  $\alpha$  chain extracellular domain having a variable domain and a constant domain, and which has a first C-terminal dimerization peptide which is heterologous to the  $\alpha$  chain; and a TCR  $\beta$  chain extracellular domain having a variable domain and a constant domain, and which has a second C-terminal dimerization peptide which is heterologous to the  $\beta$  chain; wherein the first dimerization peptide and the second dimerization peptide are specifically heterodimerized to form a heterodimerization domain; wherein a disulfide bond present in native TCRs between the  $\alpha$  and  $\beta$  chains is absent; and wherein the TCR is capable of specific binding to a peptide-MHC complex at a concentration of at least 40  $\mu$ g/ml.

Chang *et al.* disclose, in relevant part, soluble TCR constructs which consist of truncated native TCR  $\alpha$  and TCR  $\beta$  chain extracellular regions (including the cysteine

residues required to form the native disulfide interchain bond) fused to C-terminal leucine zipper peptides. The TCR-leucine zipper fusions consisted of the TCR variable regions and the extracellular TCR constant regions terminated one amino acid C-terminal of the cysteine residues involved in the formation of the native interchain disulfide bond. As noted in the Office Action, "Chang et al do not teach that a disulfide bond present in native TCRs between the alpha and beta chain is absent in the recombinant TCR having both the alpha and beta variable and constant domains" (*see*, Office Action, page 16, first full paragraph).

Gregoire *et al.* teach chimeric TCR-antibody  $\kappa$  chain proteins including a first chain comprising a TCR V $\alpha$  domain, a TCR C $\alpha$  exon 1 domain and an immunoglobulin C $\kappa$  domain, and a second chain comprising a TCR V $\beta$  domain, a TCR C $\beta$  exon 1 domain and an immunoglobulin C $\kappa$  domain. As noted in the reference, the cysteines involved in interchain disulfide bond formation in native TCRs are present in the C $\alpha$  exon 2 and C $\beta$  exon 2 domains and, therefore, the construct of Gregoire *et al.* lacks those cysteines and does not form an interchain disulfide bond between the TCR domains. However, the constructs of Gregoire *et al.* lack not only the cysteines, but all of the residues encoded by the second exon of the C $\alpha$  and C $\beta$  domains. Moreover, the -COOH termini of the C $\alpha$  and C $\beta$  exon 1 domains are joined to the -NH<sub>2</sub> termini of C $\kappa$  domains to form a structure which Gregoire *et al.* calls "illegitimate" (page 8080, first column, line 24). As explained in Gregoire *et al.*, and with reference to Figure 4(b), in the normal quaternary structure for paired C domains, "the NH<sub>2</sub> termini of C regions are far apart (> 40Å), whereas their COOH termini are close to each other and constrained by a disulfide bond" (page 8080, first column, lines 18-20). If, however, Gregoire *et al.* had employed complete C $\alpha$  and C $\beta$  domains which formed a disulfide bond near their C termini, the disulfide bond would have prevented the - NH<sub>2</sub> termini of the C $\kappa$  domains from assuming their normal positions spaced far apart. Indeed, Gregoire *et al.* speculate that "the unique ability of our construction to form  $\alpha\kappa$ - $\beta\kappa$  dimers may be due to the lack of the cysteine residue located COOH-terminal to the end of the C $\alpha$  and C $\beta$  regions and normally involved in the constitution of a constricting interchain disulfide bond" which would have disrupted the normal C $\kappa$  pairing.

Thus, one of ordinary skill in the art would understand from Gregoire *et al.* that the use of a pair of C $\kappa$  domains as dimerization domains presents particular problems of

quaternary structure because the - NH<sub>2</sub> termini must be spaced far apart and, therefore, when using C $\kappa$  domains to facilitate pairing of TCR V and C domains, the portion of each TCR C $\alpha$  and C $\beta$  domain encoded by exon 2 should be deleted. This has no bearing whatsoever upon Chang *et al.*, because those authors were not using C $\kappa$  domains as dimerization domains and, therefore, there is no motivation to combine the teachings of the references.

Moreover, the teachings of Gregoire *et al.* leave serious questions regarding the functionality of their molecule. Note in particular the dotted lines in Figure 4(b) between the C $\alpha$  and C $\beta$  domains and the C $\kappa$  domains. With respect to these, Gregoire *et al.* note: "In both of our chimeric chains, the COOH terminus of a TCR C domain has to be fitted onto the NH<sub>2</sub> terminus of a C $\kappa$  domain. Such an illegitimate interaction may distort the proper pairing of the C $\kappa$  domains and accordingly their ability to be disulfide linked." Unstated by Gregoire *et al.* is that such an illegitimate pairing may distort the proper pairing of the TCR  $\alpha$  and  $\beta$  domains and accordingly their ability to bind MHC-peptide complexes. Indeed, in the constructs of Gregoire *et al.*, as explained in the "Materials and Methods" section, the C $\alpha$  and C $\beta$  exon 1 domains are joined directly to the C $\kappa$  domains and, therefore, the dotted junctions shown in Figure 4(b) do not exist. Rather, the domains are directly joined and the quaternary structure shown in Figure 4(b) is impossible. Therefore, one of ordinary skill in the art would ask whether the soluble TCR construct of Gregoire *et al.* can be functional.

Unfortunately, this question cannot be answered because Gregoire *et al.* do not provide any binding data whatsoever for their constructs (*see*, the abstract, as well as the last paragraph on page 8081). Rather, they show that known antibodies to the C $\alpha$  (H28-710), C $\beta$  (H57-597) and C $\kappa$  (H139-52.2) domains can react with the chimeric molecule. None of these antibodies, however, are reactive with the variable domains involved in binding MHC-peptide complexes. In addition, the antibodies raised by Gregoire *et al.* against the chimeric molecules (B20.1, B20.2 and B20.6) were not tested against native TCRs. Accordingly, this document does not demonstrate that removal of the disulfide bond encoded in exon 2 of the C $\alpha$  and C $\beta$  chains results in correct TCR  $\alpha$  and  $\beta$  chain pairing, and does not provide any teaching or suggestion to one of skill in the art as to what effect removal of the interchain disulfide bond from the Chang *et al.* construct will have.

Therefore, (1) because Gregoire *et al.* used "illegitimate" constructs forcing a junction between C $\alpha$ /C $\beta$  and C $\kappa$  domains with quaternary structure requirements irrelevant to Chang *et al.* and (2) because Gregoire *et al.* did not provide any data showing binding to MHC-peptide complexes of their chimeric molecules, Gregoire *et al.* provides no motivation for one of skill in the art to remove the disulfide bond in Chang *et al.* Furthermore, given the large structural differences in the constructs of Gregoire *et al.* and Chang *et al.*, there would be no reasonable expectation of success if one were to modify the TCR constant domains of Chang *et al.* according to Gregoire *et al.*

Applicants further note that Gregoire *et al.* was published in 1991 and was available to Chang *et al.*, yet Chang *et al.* did not attempt to make a construct without an interchain disulfide bond.

The deficiencies of Gregoire *et al.* are not overcome by either, or both, the Wulffing *et al.* or Garboczi *et al.* references. Wulffing *et al.* discloses three single chain TCR (scTCR) constructs consisting of approximately 115 residues from both TCR  $\alpha$  and  $\beta$  variable regions linked by a linker peptide. In addition, it discloses that these scTCR constructs can be dimerized using a coiled coil to make a bivalent molecule. In these latter two TCRs, the coiled coil domains are not used to hold together the  $\alpha$  and  $\beta$  chains, but rather to associate the respective scTCRs. In addition, the coiled coil domains (scdHLX) form a homodimer. Thus, the central teaching of Wulffing *et al.* relates to single chain TCRs. It teaches nothing about soluble TCRs which include constant domains in the  $\alpha$  and  $\beta$  chains, as in the present invention. In particular, because the Wulffing *et al.* constructs use a peptide linker to join the  $\alpha$  and  $\beta$  chains, it teaches nothing about the non-covalent association of the  $\alpha$  and  $\beta$  chains. In fact, it teaches that the chains must be associated covalently, teaching towards the inclusion of the native disulfide bond and teaching away from the present invention.

Garboczi *et al.* disclose expression of the extracellular portions of the TCR  $\alpha$  and  $\beta$  chains truncated immediately before the cysteine residues which form the native interchain disulfide bond, followed by refolding *in vitro*. The Office Action alleges, in relevant part, that "Garboczi et al teach that heterodimerization and antigenic specificity of TCR do not require its interchain disulfide bond" (see, Office Action, page 18, second paragraph). This assertion is simply not supported by the experiments described in this paper. Rather, the

experiments reported by Garboczi *et al.* indicate that the TCR heterodimers produced by the method of Garboczi *et al.* require the interchain disulfide bond (*see* below).

Figure 2B of Garboczi *et al.* shows the results of experiments in which "Iodoacetamide treated long forms of both subunits [were] used" (see figure legend) in polyacrylamide gel electrophoresis (PAGE) comparisons. Iodoacetamide acts to block the cysteine residues and thereby prevents disulfide bond formation. However, in none of the six lanes of the gel of Figure 2B were the iodoacetamide-treated  $\alpha$  and  $\beta$  subunits tested for heterodimer formation in the absence of a stabilizing MHC molecule and an MHC-binding peptide. In particular, the only lane which includes both the  $\alpha$  and  $\beta$  subunits (lane 6) also includes the MHC molecule (HLA-A2) and the MHC-binding peptide (Tax) which help to stabilize the heterodimer. Therefore, these experiments do not demonstrate that the  $\alpha$  and  $\beta$  subunits of Garboczi *et al.* form a heterodimer absent the interchain disulfide bond.

Figure 3 of Garboczi *et al.* shows the results of experiments in which the disulfide-bonded TCR complex from the native gel shown in Figure 2A was subjected to PAGE to confirm that it contained both the disulfide-bonded TCR and the MHC protein (HLA-A2). Lane 1 of the gel shown in Figure 3 was run under denaturing and non-reducing conditions which cause the proteins present to unfold from their native tertiary conformations, but will not disrupt any interchain disulfide bonds. The TCR-complex, including the interchain disulfide bond, forms a distinct band at approximately 60 kDa. Lane 2 of the gel of Figure 3 was run under denaturing and reducing conditions which both cause the proteins to denature and disrupt any interchain disulfide bonds. As Garboczi *et al.* state: "Under reducing conditions (Fig. 3, lane 2) the 60-kDa band is converted to a 29-kDa band likely containing both the  $\alpha$ - and the  $\beta$ -chains of the TCR" (page 5405, second column, second paragraph, lines 14-16). Thus, under reducing conditions which eliminate the interchain disulfide bond, Garboczi *et al.* show that the 60-kDa TCR heterodimer dissociates into its constituent ~29-kDa chains. Therefore, these experiments suggest that the disulfide bond of Garboczi *et al.* is necessary to heterodimer formation.

Figure 4 of Garboczi *et al.* shows the results of experiments in which the short forms of the  $\alpha$  and  $\beta$  subunits (*i.e.*, truncated forms lacking the cysteines necessary for double bond formation) were subjected to electrophoresis under denaturing conditions. In lane 1, the

proteins were run under non-reducing conditions. In lane 2, the proteins were run under reducing conditions (which would disrupt intrachain disulfide bonds). It is clear from both lanes of Figure 4 that no  $\alpha\beta$  TCR heterodimers were formed but, rather, that the  $\alpha$  and  $\beta$  subunits formed distinct bands.

Figure 5A of Garboczi *et al.* shows the results of an experiment in which the short forms of the  $\alpha$  and  $\beta$  subunits (i.e., truncated forms lacking the cysteines necessary for double bond formation) were subjected to electrophoresis under non-denaturing (native) and non-reducing conditions. In the PAGE gel shown in Figure 5A, increasing amounts of the TCR  $\alpha$  and  $\beta$  chains were run with (lanes 3, 5, 7, and 9) and without (lanes 2, 4, 6, 8) the MHC molecule (HLA-A2) and MHC-binding peptide (Tax). In each case in which the TCR  $\alpha$  and  $\beta$  chains were run alone (lanes 2, 4, 6, 8) it is clear that no  $\alpha\beta$  TCR heterodimers were formed but, rather, that the  $\alpha$  and  $\beta$  subunits formed distinct bands. In contrast, in the lanes in which the MHC molecule (HLA-A2) and MHC-binding peptide (Tax) were present with the TCR  $\alpha$  and  $\beta$  chains (lanes 3, 5, 7, and 9), it is clear that an MHC-peptide-TCR  $\alpha\beta$  complex is formed. Indeed, in none of the lanes is there a band corresponding in molecular weight to an uncomplexed TCR  $\alpha\beta$  heterodimer. Therefore, this experiment clearly suggests that an MHC molecule (HLA-A2) and MHC-binding peptide (Tax) are necessary to stabilize heterodimers between the TCR  $\alpha$  and  $\beta$  chains of Garboczi *et al.*

Figures 5B and 5C show experiments similar to that in Figure 5A (short form TCR  $\alpha$  and  $\beta$  chains tested under non-denaturing, non-reducing conditions). In each lane of these gels in which the TCR  $\alpha$  and  $\beta$  chains are present without an MHC molecule and MHC-binding peptide (i.e., lane 2 of Figure 5B and lanes 3 and 6 of Figure 5C), it is clear that no  $\alpha\beta$  TCR heterodimers were formed but, rather, that the  $\alpha$  and  $\beta$  subunits formed distinct bands.

Taken together, these results strongly suggest that the TCR  $\alpha$  and  $\beta$  chains of Garboczi *et al.* without interchain disulfide bonds do not form heterodimeric TCRs except when held in a complex with an MHC molecule and MHC-binding peptide. However, TCRs with disulfide bonds are able to exist as dimers absent the stabilizing effect of the MHC. Therefore, there is no motivation provided by the teachings of Garboczi *et al.* to modify the soluble TCRs of Chang *et al.* by removing the interchain disulfide bond. Instead, Garboczi *et al.*, teach away from excluding the interchain disulfide bond.

Applicants further note that the Chang *et al.* construct ensures strong association between the two chains by virtue of the coiled-coil dimerization peptides, and the presence of the native interchain disulfide bond. However, Chang *et al.* does not demonstrate specific binding to the peptide-MHC complex. Hence, it is impossible to infer from Chang *et al.* the effect on peptide-MHC binding of omitting the native disulfide bridge. Garboczi *et al.* does not make the effect of such omission any more predictable because one of skill in the art simply does not know from either Chang *et al.* or Garboczi *et al.* the contribution made by the coiled-coil interactions alone to the conformation of the heterodimer, and thus to its specific binding functionality.

Put another way, the Chang *et al.* coiled coil interaction can be considered to be "A", and the Chang *et al.* native disulfide bridge interaction can be considered to be "B". One assumption can be that the Chang *et al.* construct actually does bind peptide-MHC (this can only be an assumption, because there is no evidence of this in Chang *et al.* whatsoever). The skilled person is not taught by Chang *et al.* which of A, B and A+B is responsible for the binding conformation. Garboczi *et al.* discloses a TCR construct which binds peptide MHC without A or B, so the skilled person is not taught by Garboczi *et al.* either what the effect of A or B is on the binding configuration. Hence, Garboczi *et al.* does not tell the skilled person anything about the effect on peptide-MHC binding of removing B from the Chang *et al.* construct, and thus provides no motivation to do so. Another assumption can be that the Chang *et al.* construct does not bind peptide-MHC. Since the Garboczi *et al.* construct binds peptide-MHC without A or B, it does not tell the skilled person anything about the effect on peptide-MHC binding of removing B from the Chang *et al.* construct. Specifically, Garboczi *et al.* does not predict that removing B will turn the Chang *et al.* construct into a binding configuration held by A alone.

In summary, Applicants respectfully assert that Chang *et al.*, in view of Gregoire *et al.*, Garboczi *et al.*, and Wulffing *et al.* either alone, or in combination, does not render obvious Applicants' claimed invention. As discussed above, both Wulffing and Garboczi teach away from Applicants' claimed invention, while Gregoire, which is directed to bringing TCR chains together through homodimerization mediated by antibody κ chains, does not teach or suggest the effect of removing the interchain disulfide bond in Chang, where the TCR chains

are brought together by heterodimerization. Also, Gregoire provides no teaching regarding the ability of their construct or Chang's construct modified to lack the interchain disulfide bond to bind MHC-peptide.

For the foregoing reasons, Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

(b) The Office Action rejected claim 28 as being obvious under 35 U.S.C. § 103(a) over Chang *et al.*, in view of Gregoire *et al.*, Garboczi *et al.*, and Wulffing *et al.*, and further in view of U.S. Pat. No. 5,643,731 or U.S. Pat. No. 5,582,996 (*see*, Office Action, pages 20-22).

Applicants respectfully traverse this rejection because Chang *et al.*, in view of Gregoire *et al.*, Garboczi *et al.*, and Wulffing *et al.* do not render obvious Applicants' claimed invention for the reasons outlined above. Neither U.S. Pat. No. 5,643,731 nor U.S. Pat. No. 5,582,996 cures the deficiencies of these references. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

(c) The Office Action rejected claim 30 as being obvious under 35 U.S.C. § 103(a) over Chang *et al.*, in view of Gregoire *et al.*, Garboczi *et al.*, and Wulffing *et al.*, and further in view of Arcone *et al.* (*see*, Office Action, pages 22-23).

Applicants respectfully traverse this rejection because Chang *et al.*, in view of Gregoire *et al.*, Garboczi *et al.*, and Wulffing *et al.* do not render obvious Applicants' claimed invention for the reasons outlined above. Arcone *et al.* does not cure the deficiencies of these references. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

(d) The Office Action rejected claims 31-32 as being obvious under 35 U.S.C. § 103(a) over Chang *et al.*, in view of Gregoire *et al.*, Garboczi *et al.*, and Wulffing *et al.*, and further in view of U.S. Pat. No. 5,635,363 (*see*, Office Action, pages 23-25).

Applicants respectfully traverse this rejection because Chang *et al.*, in view of Gregoire *et al.*, Garboczi *et al.*, and Wulffing *et al.* do not render obvious Applicants' claimed invention for the reasons outlined above. U.S. Pat. No. 5,635,363 does not cure the

deficiencies of these references. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

**CONCLUSION**

Claims 22-34 were pending in the instant application. After entry of the present amendments, claims 22 and 25-35 are pending.

Applicants respectfully request reconsideration and allowance of the claims of the instant application. If the Examiner believes that any further discussion of this communication would be helpful, she is encouraged to contact the undersigned at the phone number listed below.

Applicants petition for a three-month extension of time to respond to the Office Action. Other than the three-month extension of time fees, no additional fees are believed to be due in connection with this communication. However, if any additional fees are due, please apply any additional charges, or credit any overpayment, to our Deposit Account No. 08-0219.

Respectfully submitted,  
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Reply to Office Action of 04/09/2004

Amdt. and Resp. under 37 C.F.R. § 1.111 dated 10/12/04  
PATENTS  
Attorney Docket No: 102286.409US4

**APPENDIX A**  
**A copy of a Substitute Specification**